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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/647,654	08/25/2003	Philip W. Ingham	HMSU-P17-006	5276

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FISH & NEAVE IP GROUP  
ROPES & GRAY LLP  
ONE INTERNATIONAL PLACE  
BOSTON, MA 02110-2624

EXAMINER
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BRANNOCK, MICHAEL T

ART UNIT	PAPER NUMBER
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1649

DATE MAILED: 10/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 10/647,654	<b>Applicant(s)</b> INGHAM ET AL.	
	<b>Examiner</b> Michael Brannock	<b>Art Unit</b> 1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 26 July 2006.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-3,5,6,11-13,23-26,29,30 and 33-56 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3,5,6,11-13,23-26,29,30 and 33-56 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 August 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>021306, 021404</u> . | 6) <input type="checkbox"/> Other: _____  |

## DETAILED ACTION

### *Status of Application: Claims and Amendments*

Applicant is notified that the amendments put forth on 7/26/2006, 2/9/2004, 8/25/2003, have been entered in full.

Claims 1-3, 5, 6, 11-13, 23-26, 29, 30, 33-56 are pending. Further, the claims will be examined only to the extent that they read on *in vivo* methods of modulating neural cells with sonic hedgehog polypeptides and as the claims may read on anoxia induced ischemia, the requirement having been traversed in the response of 7/26/2006.

The traversal is on the grounds that a search of the groups would not be a serious burden on the examiner. This is not found persuasive for the following reasons:

Under MPEP § 803, there are two criteria for a proper requirement for restriction between patentably distinct inventions:

(A) The inventions must be independent (see MPEP § 8702.01, 806.04, 808.01) or distinct as claimed (see MPEP § 806.05- §806.05(I)): and

(B) There must be a serious burden on the examiner if restriction is required (see MPEP § 803.02, § 806.04(a)- 806.04(I), § 808.01(a), and § 808.02).

Consistent with current patent practice, a serious search burden may be established by (A) separate classification thereof: (B) a separate status in the art when they are classifiable together: (C) a different field of search. These criteria were met in the above restriction.

Further, a search is directed not only to art which would be anticipatory, but also to art that would render the invention obvious. In the instant case, the two method groups are considered patentably distinct because the two methods require substantially different consideration based

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upon the location and circumstances of treatment. For example, the modulating *in vivo* activity of a particular product requires consideration of the medical condition which would necessitate such treatment, efficacy (e.g. route of administration, dosage amounts, possible interactions with other body compounds and physiological systems) and ability to reach the cellular target. Such considerations are not required for the analysis of methods for product modulating activity in a defined *in vitro* environment, which requires separate considerations with regard to obviousness and enablement including media determination, substrate, and other conditions for growth of target cells and use of the claimed method in culture. The two inventions, therefore, are patentably distinct and although a search of one may overlap that of the other, the search of one could not be relied upon, solely, to provide art that is anticipatory or would render obvious the invention of the other, and to search both inventions would be burdensome.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 23, 25, 26, 29, 36-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims require the term "hedgehog polypeptide" without reference to specific amino acid sequences are indefinite because the instant specification does not identify that material element or combination of elements which is unique to, and therefore, definitive of "hedgehog

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polypeptide". An artisan cannot determine what limitations are placed upon a claim by the presence of this term.

Additionally claim 25 requires a "bioactive" fragment which the specification refers to as a fragment of a hedgehog polypeptide, wherein the encoded polypeptide specifically agonizes or antagonizes inductive events mediated by wild-type hedgehog proteins. The hedgehog bioactive fragment preferably is, for example, at least 5, 10, 20, 50, 100, 150 or 200 amino acids in length. However, the specification has not established what are and are not "inductive events mediated by wild-type hedgehog proteins", thus the skilled artisan could not be reasonably sure that he or she were practicing the claimed invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5, 6, 11-13, 23-26, 42-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of promoting growth, differentiation and/or survival of embryonic neuronal cells by administering a polypeptide (sonic hedgehog) of SEQ ID NO: 8, 11, 12, and 13 or an N-terminal autoproteolytic portion thereof (as described in the specification), does not reasonably provide enablement for administering a polypeptide other than a polypeptide of SEQ ID NO: 8, 11, 12, and 13, nor for the administration of portions of the polypeptides other than that of the N-terminal autoproteolytic portion, and nor does the specification provide enablement for promoting growth, differentiation and/or survival of neuronal cells other than embryonic cells, e.g. treating an neurodegenerative disease. The

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specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The claims encompass methods of promoting one or more of growth, differentiation and survival of adult neuronal cells in culture. The specification provides that neuronal cells grown in culture, including those from adult tissue, readily lose their differentiated state (see page 59, line 18). Also, the specification puts forth that hedgehog proteins can be added to cultures of cells in order to maintain the integrity of a culture of terminally differentiated neuronal cells by preventing loss of differentiation (see page 59, lines 22-25). Additionally, the specification provides examples of the use of sonic hedgehog in the promotion of growth, differentiation, and survival of embryonic neuronal cells. It is known that sonic hedgehog is endogenously expressed in embryos, and one of skill in the art would therefore expect that embryonic tissues would be responsive to sonic hedgehog. However, the specification also discloses experiments that indicate sonic hedgehog is not expressed in adult tissues (see page 110, lines 10-11). One of skill in the art would therefore expect that adult tissues would not be responsive to sonic hedgehog in the same way that embryonic tissues are, or perhaps not responsive at all. The specification has provided no guidance as to the nature of the response of adult tissues to sonic hedgehog. Therefore, one of skill in the art would be required to perform undue trial and error experimentation in order to determine which of the multitude of adult neural cells is responsive to sonic hedgehog. Furthermore, Triffort et al., *Journal of Neurochemistry* 70(1327-1330)1998, describe the state of the art as follows: "The roles of HH signaling in adult vertebrates have been poorly documented so far, particularly in the brain where Ptc and Smo transcripts have been identified", see the last paragraph of col 1 of page 1327. Thus, even if it is agreed that the artisan

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would be motivated to look for effects of hedgehog proteins in the adult nervous system, the artisan would be required to perform extensive research and investigation to determine what cell types were amenable to manipulation with sonic hedgehog. Further, Miao et al., J.

Neuroscience, 17(15)5891-5899, 1997 state that “there is no direct correlation between the neuron phenotypes induced by Shh and those supported by Shh in a trophic manner”, see col 1 of page 5898. Thus, the particular teachings in the specification regarding embryonic expression of hedgehog and manipulation of embryonic tissues could not be expected to provide the artisan with the knowledge required to manipulate adult tissues.

Additionally, the claims encompass an almost limitless number of polypeptides that comprise a portion of SEQ ID NO: 8, 11, 12, or 13, or comprise variants or portions of variants having a recited degree of identity to SEQ ID NO: 8, 11, 12, or 13. The specification sets forth that variants and portions can be used in the claimed methods, however, the specification does not provide sufficient guidance as to which of these variants and portions can actually be used to practice the claimed invention (see page 26 for example).

One of skill in the art is left to extensive experimentation wherein amino acids are randomly changed, deleted, or added to a polypeptide of SEQ ID NO: 8, 11, 12, or 13, and through trial and error experimentation is left to determine when a polypeptide is obtained that could used to promote neural cell growth, differentiation and/or survival. Such extensive random trial and error experimentation is considered undue.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any

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given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2. Guo-HH et al. PNAS 101(25)9205-9210, 2004, recently reviewed the art and conducted an extensive study on the effect of amino acid substitution on the functionality of a wide variety of proteins and found that on average a single amino acid substitution had a 34% chance inactivating the functionality of the protein, see the Abstract.

Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active variants or portions that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be

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active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Due to the large quantity of experimentation necessary to generate the almost limitless number of variants and portions required by the claims and screen same for activity, and to determine which, if any adult neural cells would respond to such, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function and the lack of information regarding adult neural cell responses to hedgehog proteins, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 29, 30, 33-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims require methods of treating a multitude of neurodegenerative disorders, most of which are known in the art to be severely recalcitrant to effective treatment, e.g. Alzheimer's disease, Parkinsonism, ALS etc.. The specification has simply presented the results of experiments with chicken embryonic tissue and attempts to extrapolate these findings to methods of treatment for these disorders. However this is not adequate teaching to practice the claimed methods. As discussed above, Triffort et al., Journal of Neurochemistry 70(1327-1330)1998, describe the state of the art

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as follows: “The roles of HH signaling in adult vertebrates have been poorly documented so far, particularly in the brain where Ptc and Smo transcripts have been identified”, see the last paragraph of col 1 of page 1327. Thus, even if it is agreed that the artisan would be motivated to look for effects of hedgehog proteins in the adult nervous system, the artisan would be required to perform extensive research and investigation to determine what cell types were amenable to manipulation with sonic hedgehog. Further, Miao et al., J. Neuroscience, 17(15)5891-5899, 1997 state that “there is no direct correlation between the neuron phenotypes induced by Shh and those supported by Shh in a trophic manner”, see col 1 of page 5898. Thus, the particular teachings in the specification regarding embryonic expression of hedgehog and manipulation of embryonic tissues could not be expected to provide the artisan with the knowledge required to manipulate adult tissues and treat such recalcitrant disorders as those claimed.

Due to the large quantity of experimentation necessary to determine how to treat the recited disorders, if such can be found, the lack of direction/guidance presented in the specification regarding which structural features of the hedgehog polypeptides are required in order to provide activity for any specific disease state, the absence of working examples directed to same, the complex nature of the invention which requires unknown treatment methodologies for recalcitrant disorders, the state of the prior art which is equivocal about any role for hedgehog proteins in adult neural tissues, and the breadth of the claims which encompass a genera of complex neuronal disorders having divergent etiologies and known treatment strategies, undue experimentation would be required of the skilled artisan to make the claimed invention.

Claims 1-3, 5, 6, 11-13, 23-26, 29, 30, 33-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. As discussed above, regarding claims 1-3, 5, 6, 11-13, 23-26, 42-56, there is no description of methods of promoting growth, differentiation, or survival of adult neural cells, yet the claims encompass such and are contemplated in the specification.

To determine whether there is correspondence between the generic invention of the claims and the written description, is necessary to determine whether the description conveys to one skilled in the relevant art that applicant was in possession of the claimed genus at the time the application was filed. To this end, it is appropriate to inquire whether a number of species representative of the genus are described in complete structural terms or, alternatively, with reference to other identifying characteristics, *e.g.*, partial structure, chemical properties, functional properties, *etc.* What constitutes a “representative number” of species for any given genus depends in part on whether the level of skill in the art, the teachings in the disclosure, or teachings in the prior art establish predictability as to the structural properties characteristic of the genus.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*.” (See page 1117.) The specification does not “clearly allow persons of

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ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116).

The description of growth, differentiation, or survival promoting activity of hedgehog proteins on embryonic chicken tissues does not support the claimed genera of methods that would not be expected to behave the same way, see above. Furthermore, there appears to be no specific descriptions of treatment regimes as claimed in claims 29, 30, 33-41, see above. Thus the skilled artisan would not recognize that applicant was in possession of the genera of methods claimed in claims 1-3, 5, 6, 11-13, 23-26, 42-56, nor of any particular embodiments as claimed in claims 29, 30, 33-41. Thus the claims do not meet the written description requirement of 35 U.S.C. 112, first paragraph.

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*Conclusion*

No claims are allowable.

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649. Please note the new central fax number for official correspondence below:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867. Official papers filed by fax should be directed to 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB



October 13, 2006



JANET L. ANDRES  
SUPERVISORY PATENT EXAMINER